Remarks

Applicant has amended claims 11-16 and 21 as noted above; no new matter has been added.

Rejections Under 35 U.S.C. 112, First Paragraph

The Examiner rejected claim 21 under 35 U.S.C. 112, first paragraph as not enabled for viral conditions, Alzheimer's diseases and solid tumors.

Applicant has deleted from claim 21 the methods of treatment directed to viral conditions and Alzheimer's Disease.

With regard to treatment of solid tumors, Applicant observes that, as stated on page 13 of the specification, solid tumors are conditions dependent on angiogenesis. The Examiner has already considered enabled the treatment of angiogenic diseases; accordingly, the treatment of solid tumors, as they depend on angiogenesis, also should be considered enabled.

The antitumor utility of the present compounds is also due to their vacuolar ATPase (V-ATPase) inhibiting activity: this activity is supported by the experiments shown on pages 37-38 of the specification.

V-ATPase is known to be involved in the genesis and development of tumors and the inhibition of this enzyme represents a known therapeutic approach for the treatment of tumors. For support on these points, Applicant relies on the following literature (the references herein cited in shortened form, are identified in full in the last page of this section of the Amendment).

(1) V-ATPases regulates cytoplasmatic pH, which is involved in tumorigenesis (Takayuchi et al., *J.Biol.Chem.*, 2002, 277(39), 36534-43).

(2) V-ATPases are functionally expressed in plasma membrane of many human tumor cells and are overexpressed in Multi Drug Resistant (MDR) cancer cells, which are richer in acidic organelles (Ma, 1992; Martinez-Zaguilan, 1993; Torigoe, 2002).

(3) Transfection with H^+-ATPase causes tumorigenic transformation in fibroblasts (Perona and Serrano, 1988; Gillies et al., 1990).

(4) V-ATPases are upregulated in cisplatin-resistant cell lines, where they maintain higher pHi and V-ATPase inhibitors, such as bafilomycin, were shown to potentiate cisplatin cytotoxicity and increase radiosensitivity (*Murakami, 2001).*

(5) In addition to modulating cytoplasmatic pHi, V-ATPases also maintain lower extracellular pH (pHe) and it is known that the extracellular pH of solid tumors is acidic (Wike-Hooley, 1984; Griffiths, 1991; Negendank, 1992; Gillies et al., 1994).

(6) The acidic cellular pH has many consequences which are germane to the etiopathogenesis of cancer:

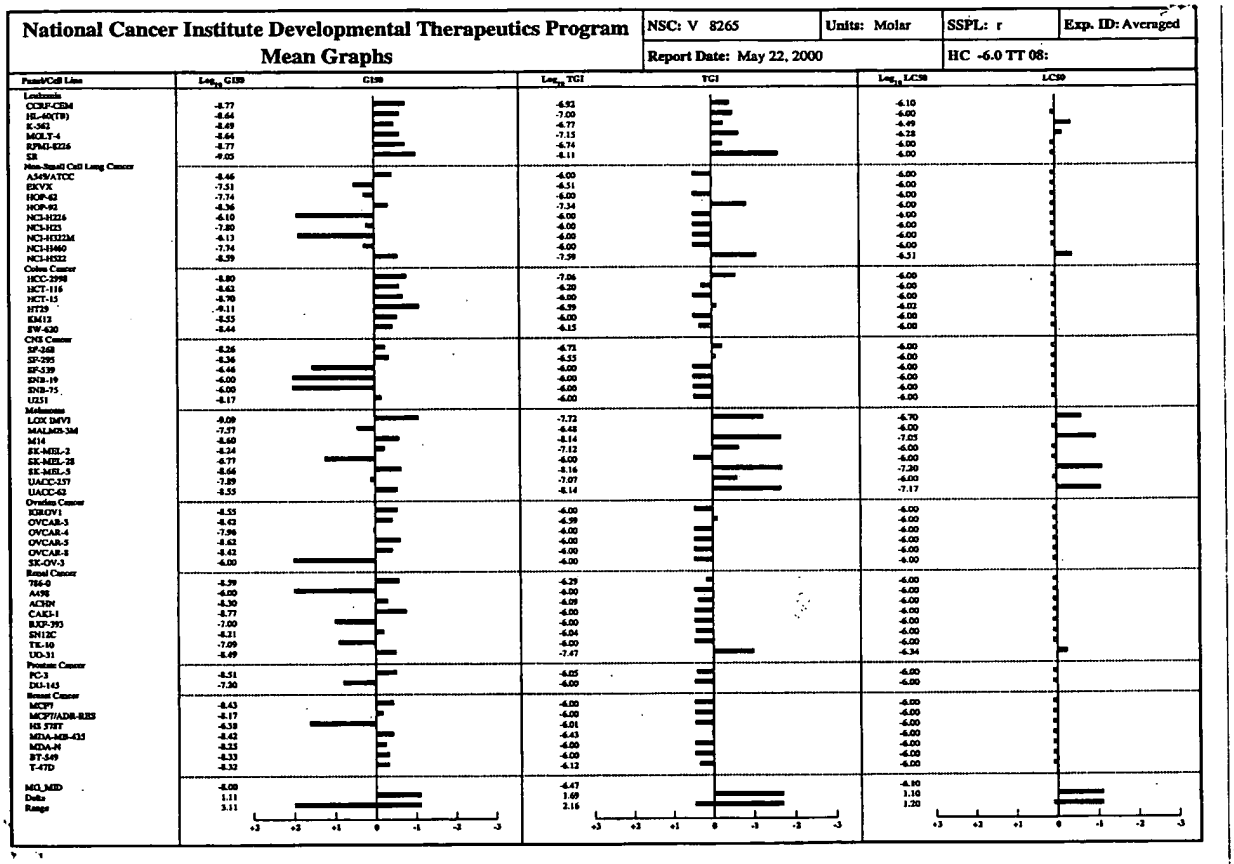
- Low pH causes tumorigenic transformation of primary Syrian hamster embryo cells (LeBoeuf et al., 1990).
- Low pH causes chromosomal rearrangements in Chinese hamster embryo cells (Morita 1990, 1992).
- Low pH induces immediate early gene expression and activates the protooncogene, ras, in kidney renal tubule cells. (Alpern, 1995; Amemiya et al., 1995).
- Low pH increases in vitro migration and invasion (Martinez-Zaguilan et al., 1996; Rozhin et al., 1994).
- Culturing cells at low pH causes them to be more metastatic in vivo (Schlappack et al., 1991)
- Low pH stabilizes some mRNA species (Hansen et al., 1996).
- Low pH induces the expression of platelet-derived endothelial cell growth factor in tumors in vivo (Griffiths et al., 1997)
- Low pH will enhance resistance to weakly basic chemotherapeutic drugs (Sognier, 1995; Simon and Schindler, 1994; Tannock and Rotin, 1989; Hahn and Shiu, 1983, 1986; Mikkelsen and Wallach, 1982).

(7) Natural products capable to inhibit the V-ATPase have displayed anti-proliferative and/or pro-apoptotic activity in vitro (Nishihara, *Biochem Biophys Res Commun* 212:255-262, 1995) and were effective in inhibiting tumor growth in vivo (Otha, *J. Pathol.* 185: 324-330, 1998). These products include bafilomycin, concanamycin, salicylhalamide, lobatamide, oximidin and apicularen. These compounds were found active in the 60 human cell line tumor screen at the National Cancer Institute, and some data are reported in Table 1.

Table 1. Anticancer potency of V-ATPase inhibitor macrolides

Compound	Mean pGI_{50}	Literature Ref.
Bafilomycin A1	8	See Fig. 1, below
Salicylhalamide	7.8	*JOC* 1997, 8188
Lobatamide	8.8	*JOC* 1998, 7805

Figure 1. Antitumor activity of bafilomycin A1 in the NCI anticancer screen



In summary, by inhibiting both angiogenesis and the activity of V-ATPase, the compounds of the present invention, inhibit tumor cell growth, tumorigenesis, metastasis,

apoptosis, and drug resistance, thereby providing a valuable method to treat tumours. In comparison with the known V-ATPase inhibitors of natural origin, the synthetically-produced indoles of the present invention represent much simpler and easily available analogues, allowing the person of skill in the art, without undue experimentation, to exploit this relevant molecular target to provide a novel and useful means to treat life-threatening cancers, including those that are resistant to the available therapies.

The Examiner also rejected claim 21 under 35 U.S.C. 112, first paragraph in paragraph 3 of the Office Action as not enabled due to its recitation of prevention of hypercholesterolemic disease. Applicant has deleted from claim 21 the reference to prevention.

Accordingly, in view of the amendment of claim 21 and the foregoing reasoned statements, Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 21 under 35 U.S.C. 112, first paragraph.

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Rejections Under 35 U.S.C. 112, Second Paragraph

The Examiner rejected claims 1-21 and 26 under 35 U.S.C. 112, second paragraph, as indefinite. Applicant has amended the claims to address some of the rejections, and respectfully traverse other of the rejections.

(a) The Examiner rejected the claims because the term "heterocyclyl" in claim 1 was alleged to be indefinite. Applicant respectfully disagrees.

Applicant respectfully notes that tthe term "heterocyclyl" is defined in the specification at page 6, lines 23-27. As stated at page 6, the size of the heterocyclyl ring is 4 to 11 ring atoms; the number of heteroatoms is 1, 2, or 3 and the nature of the heteroatoms is O, S, or N; the ring is single or fused, and may be saturated or unsaturated.

(b) The Examiner rejected the claims for the recitation in claim 1 or elsewhere of the term "substituted", which was alleged to be indefinite. Applicant respectfully disagrees for the following reasons.

Applicant respectfully submits that at each occurrence of the term "substituted", substituents for a specified substituted group are defined in the specification. For example, substituted alkyl is defined at page 6, lines 14-15, substituted heterocyclyl is defined at page 6, lines 28-29 and 17-20, substituted piperidinyl, where piperidinyl is defined as a heterocyclyl group, is defined at page 6, lines 28-29 and 17-20.

(c) The Examiner rejected claim 21 because the phrase "for example" in claim 21 was alleged to render the claim indefinite. Applicant has amended claim 21, and the claim no longer contains this phrase.

(d) The Examiner rejected claim 21 because the phrase "such as" in claim 21 was alleged to render the claim indefinite. Applicant has amended claim 21, and the claim no longer contains this phrase.

(e) The Examiner rejected claim 21 because the term "especially" in claim 21 was alleged to render the claim indefinite. Applicant has amended claim 21, and the claim no longer contains this term.

In addition to the foregoing, Applicant amended claims 11-16 to be more concise, by avoiding repeating the drawing of the same chemical formula of claim 1.

Accordingly, reconsideration and withdrawal of the rejections of the claims made under 35 U.S.C. 112, second paragraph, is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
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